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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,378	CHIRINO ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/19/2004 has been entered.

Status of Claims

2. Claims 1-19 have been canceled. Claims 20-33 are added.

Claim Rejections - 35 USC § 112, second paragraph

3. Claims 20-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons:

A. The claims recite the step of "selecting" (claim 20, step e). The method steps involved in "selecting" are not disclosed in specification, it is not clear what is being encompassed by the step.

B. Further, it is not clear how a protein resulting from step c) of claim 24 may not be with an "altered immunogenicity" - al least for the reason that this protein merely "comprises" variant amino acid sequence (meaning that it contains other, non-specified immunogenic moieties). How then the claimed method can be described as "screening" if any resulting protein is expected to have altered immunogenicity? Note that immunogenicity is broadly described in specification as follows:

> By "immunogenicity" herein refers to the ability of a protein to elicit an immune response. **The ability of a protein to elicit an immune response depends on the amino acid sequence or sequences within the protein.** Immunogenicity includes both the humoral and the cellular component of the immune response as outlined below. Amino acid sequences capable of eliciting an immune response are referred to herein as "immunogenic sequences". Preferably immunogenic sequences comprise "MHC binding sites (i.e., MHC binding motifs)", "T cell epitopes" and "B cell epitopes" as outlined below.

Examiner fully agrees that the ability of a protein to elicit an immune response depends on the amino acid sequence or sequences within the protein (highlighted above). Therefore, any product yielded by the method as claimed and having different amino acid content will inevitably have "altered" immunogenicity, and it is not clear how and what is to be selected on the last step of the method to achieve the stated objective of "screening of altered immunogenicity".

C. Claim 20 is indefinite due to the lack of clarity of the claim language failing to recite a final process step, which agrees back with the preamble. The preamble states that it is "a method of screening", however the claim recites "selecting of variant with altered immunogenecity" as final step. It is not clear how it corresponds to the "screening" objective of the method because, in Examiner's opinion, there is nothing to screen as any of the variant proteins synthesized per step d) will have altered immunogenecity (both because an immunogenic sequence is altered per step c), and because, due to "comprising" language of step d), the final variant protein contains other immunogenic sequences as well.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 20-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the

application was filed, had possession of the claimed invention. The newly submitted claims introduce new matter because, first, they recite step of "selecting variant protein with altered immuniogenicity" (claim 20, step e).There is no disclosure in the specification on the meaning and scope of the "selection" and there is no guidance on how to practice the claimed method with such method step.

Second there is no disclosure of synthesizing of variant proteins having more than one immunogenic sequence (claim 20, step d).

5. Claims 20-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to modulating of immunogenicity of proteins. There is no single example in the specification of the operability of the method neither *in silico,* nor in experimental conditions on a real protein synthesized following its *in silico* design. The only mention of "immunogenicity filter" on p. 30 (lines 15-21) is so vague that it is not clear whether applicant was in possession of any algorithm or

scoring function that would result in a design of a protein with altered immunogenicity.

The inventor must be able to describe the item to be patented with such clarity that the reader is assured that the inventor actually has possession and knowledge of the unique method that makes it worthy of patent protection. The reader can certainly appreciate the goal but establishing goals does not make a patent. As the Court of Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir.1993). To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cat*h, 935 F.3d at 1563; *see also Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"). There is no demonstration in the specification that applicants generated any compound which, after computer generation, and application of "computational immunogenicity filters" had immunogenicity different

from that of parent molecule. Similarly to *In re Wilde*r, 736 F.2d 1516 (Fed. Cir. 1984), *cert. denie*d, 469 U.S. 1209 (1985) the specification did "little more than outline] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."

Applicant argues that sufficient physical and/or chemical properties are disclosed. None of these were found in the specification. In regard to functional characteristics applicant correctly states that a sequence can be optimized using computational methods and that numerous known computerized algorithms predict binding of peptides to MHC molecules. Examiner does not dispute whether applicants were in possession of a method of determining binding to MHC molecules, however at issue is whether applicant was in possession of method of modulating immunogenicity. Discrepancy between predicted data on MHC binding and immunogenicity is well known. Thus, Meister et al. (i.e one of the methods used in the instant method, see p. 33, line 35) discusses that not all peptides predicted to bind to MHC peptides can be expected to stimulate immune response, both *in vivo* and *in vitro*. For example, only about one third (!) of peptides having motif corresponding to a given MHC allele have been found to interact with that MHC molecule. In some cases peptides which bind MHC molecules are immunodominant. See p. 598, second paragraph, and p. 582, second paragraph. Buus et al teaches

that "there are still many examples of erroneous prediction of binding at the individual peptide level; furthermore, interaction at one subsite may affect interactions at other subsites" (see paragraph bridging pages 211-212).

Section 112, first paragraph, requires the patentee to "show that an invention is complete by disclosure of substantially detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the invention. Even if the inventors were reasonably certain that immunogenicity of target protein can be modified using claimed computational methods, there is no showing in the patent that they knew that to be a fact. There is no showing of a single embodiment demonstrating modified immunogenicity. The reader can certainly appreciate the goal but establishing goals does not make a patent. As was mentioned in the rejection, the Court of Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir.1993).

Response to arguments

Applicant asserts that Examiner "acknowledged that Applicants were in possession of computational methods for optimizing sequences and predicting binding to MHC molecules". This is however, is not what was meant in the Office action which acknowledged that "applicants were in possession of a method of determining binding to MHC molecules". Determining of binding to MHC molecules is, however, unrelated to the method as claimed. As to reference to pages 44-56 which, as asserted by applicant describe methods for synthesizing and selecting variant protein, said pages are mostly dedicated to description of PCR and related methods, and not method as claimed.

6. Claims 20-33 are rejected under 35 U.S.C. 112, first paragraph, as being not enabled.

It is not clear how to use the invention as claimed. The method produces proteins that have both altered core structure (claim 20, steps a-c), more than one of said altered core structure (claim 20, step d, "at least one" language), and added other moieties (claim 20, step d, "comprising" language). The latter can be from addition of several residues (p. 36, bottom) to addition of other large proteins which, obviously, will result in a protein having different functions and immunogenicity. In

regard to alteration of the core structure, it, too, will be expected to change the functions of the target protein. This is because the peptide's structure is determined by the interplay of the hydrophobic/hydrophilic, stearic and electrostatic forces among the linked amino acid residues and It is not possible to predict the effect of replacing a single amino acid residue in a peptide's structure or bioactivity. Therefore, if replacing one or more residues in a peptide unpredictably alters its structure, this replacement also may alter bioactivity unpredictably.

In addition, the method as claimed encompasses proteins that are oligomers having plurality of altered core structure moieties (claim 20, step d, "at least one" language). It is not clear how to use such products.

There is no single example in the specification of the operability of the method neither *in silico,* nor in experimental conditions on a real protein synthesized following its *in silico* design. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 103

7. Claims 20-33 are rejected under 35 U.S.C. 103(a) as obvious over Fleckenstein et al (Eur. J. Biochem., 240, 71-77, 1996) or Abrams (Current Opinions in Immunology, 12, 85-91, 2000; references C15 and C1, respectively) in view of Altuvia et al or Meister et al or Buus et al (references C2, C37, and C9, respectively) and further in view of Mayo et al (WO 98/47089 or US Patent 6,269,312; references B1 and A1, respectively).

The instant claims are drawn to method of modulating immunogenicity of a protein comprising the steps of inputting the protein's structure into a computer, modulating the structure at variable positions, and identifying candidate variant proteins by applying "computational immunogenicity filter". The latter "filter", as explained in specification, p. 30, can be any of scoring functions derived on binding of peptides to MHC molecules, or T cell epitopes or B cell epitopes.

Fleckenstein et al (Eur. J. Biochem., 240, 71-77, 1996) teaches method for determining peptides with modulated immunogenicity (i.e., with altered binding to leucocyte antigens to MHC molecules). Peptide libraries of undecapeptides with substitutions at variable positions are prepared synthetically, and binding of the peptides to human leukocyte antigen DRB1 is used as a "immunogenicity filter" to determine variant peptide immunogenicity. Abrams teaches that to modify MHC

binding reactivity of peptides, rational targeted substitution of amino acid residues can be introduced to peptide ligands for regulation of immunogenic responses (p. 89). The referenced methods differs from the claimed invention in that both generation of variants and their testing are done in experimental conditions, not *in silico*.

There are numerous publications describing use of computerized algorithms to predict binding of peptides to MHC molecules. See, for example references of Altuvia et al or Meister et al or Buus et al, cited by applicants. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to be motivated to substitute experimental determination of the immunogenicity of the candidate variant peptides with computerized estimates of their immunogenicity, such as described in Altuvia et al or Meister et al or Buus et al.

Further, in regard to method of generating of candidate peptides, computerized way of generating peptide in the claimed method does not render the referenced methods utilizing chemical preparation of the peptides. Alternatively, computerized methods of generating peptide libraries with substitutions at variable positions proved to be an efficient way of modeling peptides which are further assessed for their biological functions. See for example, Mayo et al (WO 98/47089) or Mayo et al (US Patent 6,269,312).

Response to arguments

Examiner maintains that taken together, it would be *prima facie* obvious to one skilled in the art at the time the invention was made to be motivated to substitute experimental determination of the immunogenicity of the candidate variant peptides with computerized estimates of their immunogenicity, such as described in Altuvia et al or Meister et al or Buus et al.

Applicant argues that there is no suggestion of modifying immunogenicity *in silico* (as opposed to experimental protein modification), and there is no motivation to use computational filter. Examiner disagrees. All that is meant by "immunogenicity filter" is any scoring related to binding of peptides to MHC molecules, or T cell epitopes or B cell epitopes (specification, p. 30), can be any of scoring functions derived on binding of peptides to MHC molecules, or T cell epitopes or B cell epitopes. Abrams teaches that rational targeted substitution of amino acid residues can be introduced to peptide ligands to modify MHC binding reactivity of the ligands and regulate immunogenic responses (p. 89). Thus, the Abrams reference does suggest that targeted generation of variant amino acid sequences (i.e., as in step (b) of claim 1) is desirable to obtain candidate peptides with modified MHC binding reactivity and immunogenicity.

Further, in regard to motivation to use computational filter, the secondary references used in the rejection do suggest computerized algorithms predicting binding of peptides to MHC molecules. Thus, Buus et al teach that computational methods, especially artificial neural networks should be able to recognize peptide patterns associated with MHC binding (see p. 212, first paragraph). Altuvia et al teach computer algorithm that predicts MHC binding by considering contribution of different amino acid substitutions to MHC binding grove. (See abstract, p. 2, last paragraph). Meister et al describe computer-based algorithms for T-cell epitope prediction bey searching peptide sequences for regions that contain MHC-binding motifs. Furthermore, Brusik et al (another reference submitted by applicants) cites minimizing of experimental efforts and facilitation of identification of potential T cell epitopes as motivation for use of *in silico* MHC binding prediction methods.

Taken together, Examiner maintains that it would be *prima facie* obvious to one skilled in the art at the time the invention was made to be motivated to substitute experimental determination of the immunogenicity of the candidate variant peptides with computerized estimates of their immunogenicity, such as described in Altuvia et al or Meister et al or Buus et al.

Conclusion.

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

July 2, 2004

MICHAEL BORIN, PH.D
PRIMARY EXAMINER

mlb